REMARKS

In response to the Office Action mailed November 8, 2000, Applicant respectfully requests the Examiner to reconsider the above-captioned application in view of the foregoing amendments and the following comments.

The amended claims are shown on a separate set of pages attached hereto and entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this Amendment. On this set of pages, the insertions are underlined while the ~~deletions are stricken through~~.

I. Amendments to the claims:

Claims 60, 61, 63, 64, 65, 66, 67 and 69 have been canceled without prejudice. However, Applicants maintain that the subject matter recited in these claims is patentable and reserve full rights to pursue such subject matter in related applications.

Claims 45, 46, 58, and 70 to 73 have been amended. Claims 45, 46 and 58 have been amended solely to expedite prosecution. Claims 45, 46, 58 have also been amended so as to provide the polypeptides of SEQ ID Nos 5 and 7 and related antibody compositions in separate claims. Dependent claims 70, 71, 72 and 73 have been amended only to renumber the claim reference.

Accordingly, claims 45, 46, 58, 59, 62, 68, 70, 71, 72 and 73 are pending in this application.

II. Amendments to the specification:

Applicant submits amendments to the specification to address formal issues in the Official Action mailed November 8, 2000. The examiner noted that pages 117-124 have insufficient space for hole punching, such that holes were punched through words. Substitute pages 117-124 identical to original pages 117-124 are being submitted solely to correct informalities in page margins, thereby avoiding the obliteration of text when holes for retention tabs are punched. Accordingly, no new matter has been added.

III. Rejection under 35 U.S.C. §101:

The Examiner rejected Claims 45, 46 and 58 to 73 under 35 U.S.C. 101 asserting an absence of a well established utility, and further asserting that no substantial utilities which are specific to this protein are identified in the specification. Applicants respectfully traverse the Examiner's rejection, as the specification does provide a specific utility for the claimed polypeptide and antibody compositions. In particular, specific utility is provided in the specification for diagnosis and treatment of schizophrenia.

As noted in Example 9 of the Revised Interim Utility Guidelines Training Materials, the utility requirement is satisfied by nucleic acids encoding proteins having homology to proteins having a recognized utility. The specification points out several important characteristics of the proteins claimed in the present application which are also present in proteins associated with mental diseases. As discussed in more detail below, the specification discloses that the claimed polypeptides are homologous to the TED protein associated with mental retardation, possess CAG repeats associated with mental disease, and are encoded by a gene located in a chromosomal region implicated in schizophrenia.

A. Homology to the TED Protein

Page 11, lines 5-8, of the specification discloses that the polypeptides of the present invention have sequence homology to a gene involved in mental retardation (TED, Genbank Accession No. AF087142 (Exhibit A); Zonana J, *et al.* (1988) Am J Hum Genet 43:75-85 (Exhibit B)). On the gene and protein sequence level, the G713 gene shows a significant level of homology with a gene involved in the X-linked hypohydrotic ectodermal dysplasia (HED), and which has been named ***TED*** (Genebank Accession number AF087142 (Exhibit A)). Hypohydrotic ectodermal dysplasia (HED) affected males show mental defects, such as moderately severe mental retardation, which may be associated with hypotrichosis, abnormal teeth, and absent sweat glands. This is also provided in the specification, at page 11, ln. 5 to 12.

In view of the foregoing, Applicant respectfully maintains that the claimed polypeptides and antibodies thereto satisfy the utility requirement.

B. CAG Repeats

The specification at page 1, lines 11-13, further discloses that the polypeptides of the present invention contain repeated CAG triplet nucleotide repeats, where CAG encodes glutamine.The presence of polyglutamine repeats has been demonstrated to cause neuropsychiatric disease (Li *et al.* (1993) Genomics 16, 572-579 (Exhibit C)). An increasing

number of human neurodegenerative diseases are recognized to be caused by expansion of a CAG repeat within the protein-coding region of the disease gene. The expanded repeat encodes an expanded tract of glutamines within the protein, and whereas a normal repeat length has no pathological consequence, expansion of the glutamine tract beyond a critical threshold leads to neuronal loss and a degenerative phenotype. To date, eight glutamine-repeat diseases have been identified, including Huntington's disease (HD), spinobulbar muscular atrophy (SBMA), dentatorubral-pallidolusyan atrophy (DRPLA), and five spinocerebellar ataxias (SCAs 1, 2, 6, 7, and SCA3/MJD). These diseases all affect the nervous system and share a number of common features. First, although normal chromosomes are polymorphic with respect to repeat length, they show very low mutation rates. However, mutant chromosomes with long repeats are highly mutable and tend to increase their repeat number in successive generations. Second, as a general rule, increasing disease severity and/or decreasing age of onset of symptoms correlate with increasing size of triplet expansions. These molecular features can explain the phenomenon of anticipation, which is understood today as the tendency for the disease to manifest at an earlier age in successive generations. In particular, recent reports have suggested that anticipation may be a feature of both schizophrenia and bipolar affective disorder (Ross *et al.* (1993) TINS, 16: 254-260 (Exhibit D); Basset *et al.* (1994) Am. J. Hum. Genet., 54: 864-870 (Exhibit E); McInnis *et al.* (1993) Am. J. Hum. Genet., 53: 385-390 (Exhibit F)).

With further regards to diagnostic uses, these diseases likely share a common pathophysiology at the protein level: evidence suggests that the expanded polyglutamine tract confers a dominant, toxic property upon these otherwise unrelated proteins. The longer the repeat, the earlier the onset and the more severe the disease. For Huntington's disease (HD) in particular, several authors have shown the existence of a correlation between the number of CAG repeats present upstream the huntingtin (Huntington Disease's protein) coding sequence and both the severity and the age of onset of this pathology. For example, Brinkman *et al.* ((1997) Am. J. Hum. Genet., 60:1202-1210 (Exhibit G)) have used a large cohort of patients and their study has shown that CAG repeat length is the major determinant of age at onset in HD. By assessing the CAG size alone, these authors were able to predict the likelihood that an individual would be affected by a particular age, for the vast majority of persons tested.

A great deal of further work has been carried concerning the mechanism by which CAG repeats can cause disease, including modeling studies of the conformation structure. The above

information as well as further review of selected research is provided in the specification at page 1, ln. 29 to page 4, ln. 5.

For the foregoing reasons, Applicants respectfully maintain that the claimed polypeptides and antibodies thereto satisfy the utility requirement.

C. Location in Chromosomal Region Harboring Gene Associated with Schizophrenia

The specification at page 11, lines 1-4 discloses the localization of the G713 gene to a genomic region which has been repeatedly shown to be highly associated with schizophrenia (Blouin JL *et al.* (1998) Nature Genetics, 20:70-73 (Exhibit H); Lin MW *et al.*(1997) Hum. Genet., 99:417-420 (Exhibit I); Brzustowicz *et al.* (1999) Am. J. Hum. Genet. 65:1096-1103 (Exhibit J)). The latter information is of particular interest to establish specific utility because genetic studies have the ability to identify causal factors in disease rather than symptoms. Many linkage studies have provided evidence supporting the hypothesis that chromosome 13q is likely to harbor a schizophrenia susceptibility locus. (Pulver *et al.* (1996) Cold Spring Harb. Symp. Quant. Biol. 63:797-814 (Exhibit K); Straub *et al.* (1997) Am. J. Med. Genet. Neuropsychiatr. Genet. 74:558 (Exhibit L); and Shaw *et al.* (1998) Am. J. Med. Genet. 81:364-376 (Exhibit M))

A region that has recently shown the highest evidence of linkage is the chromosome 13q31-q33 region. Studies identifying susceptibility loci on the 13q31-q33 region include Blouin *et al*, (1998), Lin *et al.* (1997), and Brzustowicz *et al.* (1999), for schizophrenia; and Detera-Wadleigh *et al.* (1999) PNAS USA 96:5604-5609 (Exhibit N) and most recently Kelsoe *et al.* (2001) PNAS USA 98:585-590 (Exhibit O) for bipolar disorder. Blouin *et al.* (1998) for example conducted a genome wide scan for schizophrenia susceptibility loci using 452 microsatellite markers on 54 complex pedigrees. The most significant linkage between schizophrenia in families was found on chromosome 13q31-q33 region near marker D13S174. Brzustowics *et al.* (1999) evaluated microsatellite markers spanning chromosomes 8 and 13 in 21 extended Canadian families. Markers in the chromosome 13q31-q33 region produced positive LOD scores in each analysis model used: autosomal dominant and recessive, with narrow or broad definition of schizophrenia. Maximum three point LOD scores were obtained with marker D13S793 under a recessive-broad model: 3.92 at recombinant fraction (θ) .1 under homogeneity and 4.42 with α=.65 and θ=0 under heterogeneity. Detera-Wadleigh *et al.* (1999) involved bipolar disorder patients and again identified biallelic markers (including D13S779 also identified by Blouin *et al.* (1998) and Brzustowics *et al.* (1999)) located on the chromosome

13q31-33 region as linked to disease. Thus, the G713 gene located in the 13q33 region is flanked by markers showing highest significance in linkage studies.

Linkage analysis is a powerful method for detecting genes involved in a trait as it provides information on the cause of a trait. However, due to the low resolution of linkage studies (typically at the megabase level), further information about the sequence structure of the region of interest is generally needed.

Using the biallelic markers described in the specification in high resolution association analyses, Applicants have narrowed the large chromosomal region implicated in mental disease from the approximately 20Mb region identified by low resolution linkage studies down to 2 Mb. (See specification at page 11, line 19 to page 12, line 17 and page 169, line 9 to page 173, line 7). Furthermore, Applicants have identified, sequenced and characterized the G713 gene which lies within this 2Mb region. By sequencing and characterizing the G713 gene and the chromosome 13p33 region containing the G713 gene, the inventors have localized the G713 gene and have provided evidence suggesting that G713 may have a causal role in schizophrenia and/or bipolar disorder. Furthermore, as discussed above, based on gene structure alone, the polypeptides encoded by the G713 gene have several characteristics found in polypeptides associated with mental disease.

In view of the foregoing, Applicants respectfully submit that the claimed polypeptides and antibodies thereto satisfy the utility requirement.

IV. Rejection under 35 U.S.C. §112, first paragraph:

Claims 45, 46 and 58 to 73 were rejected under 35 U.S.C. §112, first paragraph on the assertion that the claims encompass genomic sequences that were not described in the specification.

Applicants request that the rejection be withdrawn. New claims as discussed above may obviate the rejection. As amended above, Claims 45, 46, and 58-73 recite polypeptides comprising SEQ ID NOs. 5 or 7 or particular portions thereof and antibodies which recognize the foregoing polypeptides. Applicants note that Example 8 of the Revised Interim Written Description Guidelines Training Materials specifies that where Applicants have identified a full length open reading frame, such as those of SEQ ID NOs.: 5 or 7, they are entitled to claim nucleic acids (or polypeptides) comprising the identified open reading frame. Accordingly,

Applicants respectfully submit that the claimed polypeptides have been adequately described in the specification. Furthermore, the specification also describes the claimed fragments of the polypeptides of SEQ ID NOs. 5 and 7 (See specification at page 118, lines 23-26)

In addition, Applicants believe that it is well settled that an applicant is entitled to claim a genus containing a large number of species falling within the genus. It is not necessary for the specification to describe every species falling within the genus. This principle is enunciated in the Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, para. 1 "Written Description" Requirement, where it is stated "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species....." (Revised Interim Guidelines for Examination of Patent Applications for Under the 35 U.S.C. §112, para. 1 "Written Description" Requirement §3(a)(2)). Likewise, the Court of Appeals for the Federal Circuit has stated " A specification may, within the meaning of 35 U.S.C. §112¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses." (*Utter v. Hiraga,* 6 U.S.P.Q.2d 1709 (Fed. Cir. 1988); See also *Application of Angstadt*, 537 F.2d 498 (C.C.P.A. 1976), and *Application of Marzocchi*, 439 F.2d 220 (C.C.P.A. 1973)).

By describing the sequences of SEQ ID Nos. 5 and 7, Applicants have described a large number of species which fall within the scope of Claims 45, 46, and 58 to 73. Because there are a large number of fragments of the disclosed cDNAs, Applicant has described a representative number of species falling within the scope of claims 45, 46, and 58 to 73. Consequently, Applicant respectfully submits that the requirements of 35 U.S.C. §112¶1 have been satisfied.

V. Rejection under 35 U.S.C. §102:

Claim 45 were rejected under 35 U.S.C. 102(b) over Wimmer *et al.* Claims 45 and 69 were rejected under 35 U.S.C. 102(a) over Bartsch *et al.*

As shown by the Examiner, both Wimmer *et al* and Bartsch *et al* disclose polyglutamine tracts of at least 6 amino acids. However, no other sequence similarities with the polypeptides of Claims 45 and 69 are shared by the proteins of Wimmer *et al* and Bartsch *et al.*

As further noted above, claims 45 and 69 submitted herewith have been amended so as to exclude amino acid sequences consisting of only polyglutamine repeats. It is therefore requested that the rejection be withdrawn.

Rejection under 35 U.S.C. §§102(b)/103(a):

Claims 45, 46 and 58 to 73 were rejected under 35 U.S.C. §102(b) or §103(a) over Hanson *et al*, disclosing a 50kD protein.

Applicants believe that the Examiner has not made a prima facie case of inherency. The Examiner has not shown that Hanson teaches any of the characteristics of the polypeptide of the claims. In addition, as recognized by the Examiner, Hanson is silent on the gene or amino acid sequence, as well as any aspect of the G713 gene and protein described in the specification.

In any event, having a molecular weight of about 50kD does not provide that the protein of Hanson is necessarily the same as the protein of the claims. One of skill in the art would expect to find that many different proteins (in a neuronal cell or other cell) that will have an apparent molecular weight of about 50kD; many different proteins can have a molecular weight of about 50kD. In just one example, Cimato TR *et al.* ((1997) J Cell Biol;138:1089 (Exhibit P)) show the presence of several 50kD polypeptides (having different isoelectric points) in neuronal (PC12) cells.

M.P.E.P provides at §2112:

*The fact that a certain result or characteristic **may** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993);*

'"To establish inherency, the extrinsic evidence `must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)(citations omitted); and

*"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)*

Applicant thus submits that the Examiner has not made a prima facie showing, and requests that the rejection of Claims 45, 46 and 58 to 73 under 35 U.S.C. 102(b) or 103(a) over Hanson *et al* be withdrawn.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

Dated: March 8, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 60, 61, 63, 64, 65, 66, 67 and 69 have been cancelled.

Substitute pages 117-124 have been provided.

Claims 45, 46, 58, and 70 to 73 have been amended as follows:

45. (amended) An isolated, purified, or recombinant polypeptide comprising ~~a contiguous span of at least 6 amino acids~~ the amino acid sequence of SEQ ID No.~~s 5 or~~ 7.

46. (amended) An isolated or purified antibody composition ~~are~~ capable of selectively binding to an epitope-containing fragment of a polypeptide according to claim 45~~, wherein said epitope comprises:~~

~~- at least one of the amino acid positions 62 to 102 or 203 to 458 of SEQ ID No. 5, and/or;~~

~~amino acid positions 1 to 467 of SEQ ID No 7.~~

58. (amended) An isolated, purified, or recombinant polypeptide comprising the amino acid sequence of SEQ ID No 5~~, or a sequence having at least 70% amino acid identity thereto.~~

70. (amended) An isolated or purified antibody composition, wherein said antibody specifically binds an epitope bearing portion of the polypeptide of claim ~~67~~ 58, wherein said epitope comprises at least one of the amino acid positions 203 to 458 of SEQ ID No. 5.

71. (amended) An isolated or purified antibody composition, wherein said antibody specifically binds an epitope bearing portion of the polypeptide of claim ~~69~~ 59, wherein said epitope comprises at least one of the amino acid positions 203 to 458 of SEQ ID No. 5.

72. (amended) A diagnostic kit for detecting *in vitro* the presence of a G713 polypeptide in a biological sample, said kit comprising:

a) a polyclonal or monoclonal antibody that specifically binds a G713 polypeptide according to any one of claims ~~59, 67 or 69~~ 45, 58 or 59 or a fragment thereof~~, optionally labeled~~;

b) a reagent allowing the detection of the antigen-antibody complexes formed between a G713 polypeptide and said antibody.

73. (amended) A method of determining whether a G713 gene product is present or absent in a biological sample comprising the steps of:

a) obtaining said biological sample from a human or non-human mammal,

b) contacting said biological sample with the anti-G713 antibody of any one of claims ~~63, 70 or 71~~ 46, 70 or 71,

c) determining the presence or absence of said G713 gene product in said biological sample.

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